Please add the following new claims 37 and 38:

B12

-- 37. (New) The method of claim 17 wherein the at least one epitope is GAD.

38. (New) The method of claim 27 wherein the at least one epitope is GAD.--

## REMARKS

The present invention provides immunomodulating compositions for use in treating or preventing autoimmune diabetes comprising a nucleic acid construct encoding at least one epitope from a self-antigen and further encoding a biological response modifier in a pharmaceutically acceptable carrier. The invention further provides methods for inducing a positive regulatory immune response in a subject having or at risk of having diabetes and methods for treating or preventing autoimmune diabetes in a subject comprising administering to the subject an immunomodulatory effective amount of a nucleic acid construct encoding at least one epitope from at least one self-antigen in a pharmaceutically acceptable carrier, wherein expression of the epitope generates in the subject a positive regulatory immune response, thereby treating or preventing the diabetes. In another embodiment, the invention provides methods for inducing a positive regulatory immune response in a subject in need thereof comprising by administering to the subject an immunomodulatory effective amount of a nucleic acid construct encoding at least one epitope from at least one self-antigen in a pharmaceutically acceptable carrier, wherein expression of the epitope generates in the subject a positive regulatory immune response.

Claims 1-36 were pending before this response. By the present communication, claims 4, 6, 15 and 25 are canceled without prejudice, claims 1, 7, 8, 11, 18, 19, 20, 22, 28-30 and 34-36 have been amended, and new claims 37-38 having been added to define Applicant's invention with greater particularity. The amendments and new claims add no new matter as the new claim

language is fully supported by the specification and original claims. Accordingly, claims 1-3, 5, 7-14, 16-24 and 26-38 are currently pending.

**The Specification**

The Examiner has requested amendment of the Specification to show proper use of the trademarks, for example ACCUCHECK III and TWEEN. In compliance, the Specification has been amended by the present communication to provide proper use of the trademarks ACCUCHECK III and TWEEN.

**The Rejection under 35 U.S.C. § 112, First Paragraph**

Applicant respectfully traverses the rejection of claims 1-31 under 35 U.S.C. § 112, first paragraph, for alleged lack of an enabling disclosure. Applicant disagrees with the Examiner's assertion that the specification does not reasonably provide enablement for treatment of any autoimmune disorder, such as diabetes. In particular, Applicant disagrees with the Examiner's assertion that "Giannoukakis et al. have taught the unpredictability *of the claimed invention*" (Office Action, page 5, emphasis added). In fact, Giannoukakis' assertions regarding the safety risks and unpredictability pertain to treatments of diabetes wherein foreign islet producing cells (for example, porcine cells or cell obtained from cadavers) are introduced into the subject, but do not, therefore, apply to the present invention. Giannoukakis' method of transplanting insulin producing cells depends for utility upon *in vivo* viability and continued function of transplanted cells in the subject's body (i.e., to produce a therapeutic amount of insulin). Because the cells are foreign, the subject's host inflammatory response tends to destroy the transplanted cells and may attack healthy islet cells as well.

Alternatively, in the embodiments of Giannoukakis' method wherein DNA is administered to a subject, the method utilizes a gene therapy-like application, wherein efficacy of the treatment requires that the gene product be expressed in the subject over an extended period of time and at substantial levels to supplement a lack of insulin. Thus, in all cases the treatment

is successfully only so long as the administered construct produces a therapeutic drug in vivo in the subject.

By contrast, in the present invention, the subject is transiently transfected (i.e. genetic immunization) with polynucleotides that encode an immunogenic substance, an antigen and, optionally, a biological response modifier, for transient expression by the subject's own cells or by a plasmid administered to the subject. Efficacy requires only sufficient expression of the foreign protein to raise "a positive regulatory immune response", thus the construct need function in the subject's body only long enough for the immune response to be triggered and booster doses may be administered, as needed, in accordance with routine practice. Studies have shown that expression by only hundreds to thousands of cells is sufficient for this purpose (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10837410&dopt=Abstract)) Continuous expression of the administered construct is not contemplated and would be counterproductive. So Giannoukakis' concerns about the subject's body rejecting foreign islet cells so as to cause immune destruction of healthy islet cells does not apply to the present invention. This is particularly true with regard to invention methods as defined by claim 22, wherein only the presence of a positive regulatory immune response is required.

In addition, in Applicant's methods no porcine cells are required to be implanted into the subject, with all the attendant inherent risks of rejection described by Giannoukakis. In fact, in many cases Applicant's nucleic acid construct can be naked DNA and can encode a purely human product.

Thus, Applicant submits that the Examiner's arguments concerning unpredictability and lack of enablement of the present invention in view of the warnings of Giannoukakis are not sufficient to support a rejection for lack of enablement under 35 U.S.C. 112, First Paragraph. Accordingly, Applicants request reconsideration and withdrawal of the rejection as applied to amended claims 1, 11 and 22.

In addition, Applicant respectfully submits that those of skill in the art could readily provide nucleic acid encoding an epitope of a self-antigen and a biological response modifier for a human subject that could be transiently transfected into a subject so as to generate "a positive regulatory immune response" in a subject to which it is administered. The Wands factors that might apply to the question of enablement of the experimental protocol disclosed by Giannoukakis are simply different that those that apply to Applicant's invention.

To reduce the issues and expedite prosecution, Applicant has amended the present claims to require treatment or prevention of autoimmune diabetes, such as type 1 diabetes. Those of skill in the art recognize that insulin and GAD are self-antigens in type 1 diabetes in humans and in spontaneous animal models (i.e., non-obese diabetic mice). Given the level of knowledge in the art at the time the present application was filed, and the guidelines in the present application, those of skill in the art would know how to prepare nucleic acid encoding an epitope of a self-antigen (especially a self-antigen known to be associated with the etiology of type 1 diabetes) and, optionally, a biological response modifier, that would be fully compatible with the subject to be treated, whether mouse or human, and which would raise a positive immune response in the subject. For example, Applicant discloses a number of different "expressed epitopes" useful for treating diabetes (Specification, page 34, lines 4-13). Additional epitopes are known in the art and will be discovered in the future. In addition, nucleic acid encoding fully human cytokines and chemokines was known at the filing date of the present invention (Specification, page 27, line 24 to page 28, line 16).

To illustrate the efficacy of the teachings in the Specification regarding use of invention constructs in treatment or prevention of autoimmune diabetes in a subject at risk of or having such diabetes, Applicant submits herewith a Declaration under 37 C.F.R. § 1.132 (attached hereto as Exhibit A) describing experiments performed since the filing date of the present application which illustrate the efficacy of the invention method for treating or preventing diabetes in non-obese diabetic (*nod*) mice, an animal model for spontaneous autoimmune diabetes that is generally accepted as reasonably predictive of outcomes in humans. As described in the Declaration, in the first experiment, tests were conducted to determine the effect of

induced peripheral expression of self-antigen (porcine insulin B chain) (InsB) on spontaneous occurrence of IDDM in *nod* mice in which diabetes occurs spontaneously in 80% of the females and 30% of the males by 30 weeks of age. The mice were administered intramuscularly a plasmid engineered to express porcine insulin B chain DNA under the control of the initial-early promoter of CMV at the age of 7 days and boosting at 4 and 8 weeks. Only around 35% of the treated mice displayed full-blown disease in contrast with the expected rate of 80% in naïve female *nod* mice.

As further described in the Declaration, intramuscular administration of the plasmid to *nod*-mice resulted in long-lasting expansion of GAD and InsB-specific T cell pool committed toward IL-4, but not IFN-γ production (Fig. 2), as shown in the spleens of diabetes-free 30-weeks old treated mice. In addition, analysis of the effect of vaccination upon the autoreactive T cell repertoire in the treated mice using an ELISA-based analysis, showed (Table 2 of Declaration) that in mice administered the InsB-containing plasmid that did not develop diabetes by 30 weeks of age, infiltrating T cells displayed increased production of IL-4 and TGF-β1, compared to naïve or control plasmid-inoculated mice. Furthermore, the infiltrating T cells from pInsB-vaccinated mice displayed reduced production of IL-1β. According to the Declaration of Dr. von Herrath, this cytokine profile indicates that in protected mice that were treated according to invention methods a modified autoreactive T cell profile was triggered consisting in a shift from Th1 to Th2 immunity, a positive regulatory immune response.

In yet another experiment described in the Declaration of Dr. von Herrath, nod mice were immunized intramuscularly with a control plasmid (100μg/dose of pCMV control) or with a mixture of two plasmids (50μg pCMV-InsB and 50μg pHTLV-IL-4, expressing insulin B and IL-4 cytokine, as described above. Only about 20% of the nod mice treated by inoculation with polynucleotides encoding Ins-B and IL-4 developed symptoms of diabetes by age 18 weeks as compared with over 45% of the control mice.

Thus, Applicant has presented examples from two distinct models of the treatment of autoimmune diabetes using invention methods: a transgenic model contained in the Examples of the original Specification and a spontaneous model of autoimmune diabetes in the nod mouse. Applicant respectfully submits that the results of these experiments confirm that the teachings in the Specification are sufficient to enable those of skill in the art to make and use the invention.

Based upon the amendments and the above remarks, Applicant submits that the present Specification provides sufficient objective data to fully enable the subject matter of amended claims 1-3, 5, 7-14, 16-24 and 26-38 and reconsideration of the present rejection for lack of enablement is therefore respectfully requested.

**The Rejection under 35 U.S.C. § 112, Second Paragraph**

Applicant respectfully traverses the rejection of claims 6-8, 17-21, 27-29, 30 and 36 under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. With regard to the Examiner's assertion that the term "biological response modifier" in claims 6, 17 and 27 is allegedly "not an art recognized term and no definition is provided in the claims and specification " (Office Action, page 5), Applicant respectfully submits that the Specification provides a general functional description of the term as used in the claims at issue. The Specification teaches that biological response modifiers (BRMs) are a variety of "immunopotentiating agents" that stimulate the immune system without specificity (Specification, page 26, lines 24-25), including "agents that may not be immunogenic to the host, but nevertheless potentiate immunity by activating or enhancing the activity of cells of the immune system (Specification, page 27, lines 25- 26). Since the Specification provides a general functional description of the term, Applicants disagree with the Examiner's assertion that the term is defined in the Specification only by a "few examples."

In addition, Applicants respectfully submit that the term "biological response modifier" was well known to those of skill in the art at the filing date of the present application. In fact, the

Cancer Research Institute of the National Institute of Health propounded a letter of intent on October 30, 1995 entitled "Cancer Therapy with Biological Response Modifiers" (RFA: CA-95-017) (copy attached) making available grants for study of BMRs in treatment of cancer. In addition, Applicants attach a page from the web site of the Cancer Research Institute (www.cancerresearch.org/immpower.html) wherein "biological response modifiers" is defined as subjects intrinsic to the body "that affect the immune response." Thus, the meaning of the term "biological response modifier" was well known to those of skill in the art at the filing of the present application.

Therefore, in view of the clear definition of the term in the Specification and the general knowledge of the term by those of skill in the art, Applicants submit that Applicants' use of the term "biological response modifier" in amended claims 6, 17 and 27 is definite under the statute.

With regard to claim 9, the Examiner asserts that there is insufficient antecedent basis for the terms "nucleic acid construct" in line 2 and "biological response modifier" in line 3. However, Applicant respectfully submits that claim 9 depends from claim 1, which recites the term "a nucleic acid construct, " thus providing proper antecedent basis for the term "*the* nucleic acid construct in dependent claim 9. In addition, claim 1 has been amended to require a biological response modifier, thus providing proper antecedent basis for the term "*the* biological response modifier" in dependent claim 9.

With regard to claim 20, the Examiner alleges a lack of antecedent basis for the term "biological response modifier" in line 3 thereof. However, Applicants submit that amended claim 20 depends from amended claim 17, which recites the term "a biological response modifier," thus providing proper antecedent basis for the term "*the* biological response modifier" in line 3 of dependent claim 20.

With regard to claim 29, the Examiner alleges a lack of antecedent basis for the term "biological response modifier" in line 1 thereof. However, Applicants submit that amended

claim 29 depends from amended claim 27, which recites the term "a biological response modifier." Thus proper antecedent basis for the term "*the* biological response modifier" in claim 29 is provided by claim 27, from which it depends.

With regard to the rejection of claim 30 as allegedly being indefinite due to use of the phrase "regulatory element," claim 30 has been amended herein to further define the meaning of the term "regulatory element" therein by inserting the requirement that the regulatory element is "operatively linked to nucleic acid encoding the at least one epitope or the biological response modifier and/or the biological response modifier." Thus, as amended by this communication, the language of claim 30 parallels that of claims 9 and 20, which were not included in the present rejection.

Applicants respectfully traverse the Examiner's assertion that the term "non-pathogenic ... Th lymphocytes" allegedly renders claim 36 indefinite because the term is "not an art recognized term" (Office Action, page 7). Applicants respectfully submit that in the context of the subject matter of the present application (i.e., the treatment of T-cell mediated autoimmune disease), the meaning of the term "non-pathogenic ... Th lymphocytes" would be clear to those of skill in the art. Webster's II New College Dictionary defines "pathogenic" as "capable of causing disease." Therefore, Applicants respectfully submit that in the context of all the teachings in the Specification, those of skill in the art would understand that "a non-pathogenic" T helper cell is simply one that does not contribute to the autoimmune (i.e., pathogenic) condition being treated, for example a Th2 lymphocyte.

In view of the above amendments and arguments, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 6-8, 17-21, 27-29, 30 and 36 under 35 U.S.C. § 112, Second Paragraph.

**The Rejection under 35 U.S.C. § 102**

Applicant's invention immunomodulating composition for use in treating or preventing diabetes, as defined by present claim 1, distinguishes over the disclosure of each of the allegedly anticipating references cited by comprising a nucleic acid construct encoding at least one epitope from a self-antigen in a pharmaceutically acceptable carrier and a biological response modifier. Applicant's invention method for treating or preventing autoimmune diabetes in a subject having or at risk of having the diabetes, as defined by claim 11, distinguishes over the disclosure of each of the allegedly anticipating references cited by requiring administration to the subject of an immunomodulatory effective amount of a nucleic acid construct encoding at least one epitope from a self-antigen," wherein expression of the construct in the subject generates a positive regulatory immune response, thereby treating or preventing the diabetes." Applicant's invention method for inducing a regulatory immune response in a subject having or at risk of having diabetes, as defined by claim 22, distinguishes over each of the allegedly anticipating references cited by requiring administering to the subject an immunomodulatory effective amount of a nucleic acid construct encoding at least one epitope from a self-antigen in a pharmaceutically acceptable carrier, wherein expression of the epitope in the subject generates a positive regulatory immune response.

Thus, Applicant's invention, as defined by amended claims 1, 11 and 22, pertains to treatment or prevention of autoimmune diabetes by administering a nucleic acid construct to the subject so as to stimulate a "positive regulatory" immune response (e.g., a Th2 response). Applicants teach that stimulations of a positive regulatory immune response to the self-antigen results in treatment of an already existing disorder or in preventing development of autoimmune diabetes in an individual at risk of developing the disorder. Applicant defines a "self-antigen epitope" as follows:

> ... a peptide or protein against which an immune response can be elicited. The self-antigen epitope(s) is an immunogenic peptide protein fragment or protein derived from an autoreactive antigen or a cell involved in autoimmune disease. The immune response directed against the epitope or protein will protect the

individual against the specific infection or disease with which the self-antigen epitope(s) is associated.

(Specification, page 12, lines 26-31). In addition, as is well understood in the art, each autoimmune disease is characterized by an immune response in the host directed at one or more "self antigens"; whereas in the absence of autoimmune disease there are no active immune responses to self antigens, and no symptoms appear (See, WO 97/46253, page 17, of record herein).

**A. The Liu Reference**

Applicants respectfully traverse the rejection of claims 1, 2, 5, 9-11, 13, 14, 16, 20-24, 26 and 30-36 under 35 U.S.C. § 102(a) for allegedly being anticipated by Jingxue Liu et al. (*Gene Ther Mol Biol* 3:197-206, 1998; hereinafter "Liu"). In contrast to Applicant's immunomodulating compositions, as described above, Liu discloses a nucleic acid construct encoding a truncated version of human glutamic acid decarboxylase 65 (GAD65) and the leader peptide (i.e., the first 23 amino acids) of IL-2 (See Liu, Materials and Methods, page 203). The function of the IL-2 leader peptide in the prior art construct is to cause secretion by mammalian cells of normally intracellular proteins (See Liu, page 198, Col 2). Liu fails to disclose that the IL-2 leader peptide functions as a "biological response modifier" (i.e., possesses the cytokine function of IL-2) and, indeed, it does not. Thus Applicant respectfully submits that Liu fails to disclose a nucleic acid construct encoding both an epitope of a self-antigen and a biological response modifier, such as a cytokine or a chemokine.

Applicant respectfully disagrees with the Examiner's conclusion that Liu's disclosure anticipates the invention composition of amended claim 1 or the invention methods of claims 11 and 22 (and all claims dependent thereon). Liu administered GAD-expressing CMV plasmids to *nod* mice and observed a reduction in insulitis, not autoimmune diabetes. Although prevention of diabetes is frequently associated with a reduction in insulitis, Applicant respectfully submits that scientific studies have repeatedly shown that prevention of diabetes cannot be predicted based on

insulitis scores, as is done by Liu. Indeed, there are two types of insulitis, benign and destructive insulitis, which do not correlate with the magnitude of the islet infiltration, but constitute qualitative differences between infiltrating lymphocytes and antigen presenting cells.

Therefore, Applicant respectfully submits that Liu's finding of a reduction in insulitis cannot be extrapolated as an indication of, or even a sign of decreased likelihood of, autoimmune diabetes developing. Furthermore, there are multiple examples in the literature where autoimmune diabetes is prevented while profound intra and peri-insulitis is present von Herrath *J. Clin.Invest*, 98/6:1324-1331, 1995. In view of this record in the scientific literature, it is Applicant's position that Liu has drawn a premature conclusion that has been proven by others to be erroneous.

In view of the above amendments and remarks, Applicant respectfully submits that Liu does not anticipate the invention constructs and methods, as defined by amended claims 1-3, 5, 7-14, 16-24 and 26-38, under 35 U.S.C. § 102(a).

In addition, Liu fails to suggest under 35 U.S.C. § 103 the invention nucleic acid construct, as defined by amended claim 1, encoding an epitope of a self-antigen and a functional biological response modifier. In Liu's nucleic acid construct the IL-2 derived sequence is only a "leader peptide" whose function normally is to facilitate passage through a membrane, such as insertion into membranes of the endoplasmic reticulum, as is known in the art (See for example, Lewin et al., *genes VII,* Oxford University Press, New York, 2000, Glossary). Liu fails to suggest any modification of the GAD65 containing construct to include nucleic acid that encodes a biological response modifier so as to create a positive immune response in the subject at risk of an autoimmune disease, such as type I diabetes, or to treat a subject already experiencing such an autoimmune disease. Thus, Applicant respectfully submits that Liu would also fail to suggest Applicant's compositions under 35 USC § 103.

The deficiencies of Liu for anticipating Applicant's invention methods for prevention or treatment of autoimmune diabetes apply as well here. In addition, Applicant respectfully submits that, at best, Liu's disclosure is an invitation to try the approach of testing the effect of intramuscular immunization of naked DNA in the *nod* mouse model for the purpose of treating autoimmune diabetes via gene therapy, i.e., wherein the therapeutic or preventative effect depends upon sustained expression of the construct. For example, Liu concludes that "injection of DNA encoding [GAD65] ... suggest[s] the possibility that this form of gene therapy might be useful to prevent clinical manifestation of IDDM" (Liu, page 198, Col. 2). Liu contains no suggestion whatsoever that the prior art construct could be transiently expressed to trigger a "positive regulatory immune response, thereby treating or preventing the diabetes," as required in Applicant's invention. Accordingly, Applicant respectfully submits that the methods of amended claims 11-14, 16-24 and 26-38 are not *prima facie* obvious in view of Liu.

B. WO 97/46253

Applicant respectfully traverses the rejection of claims 1-9, 11-20, 22-30 and 32-36 under 35 U.S.C. § 102(b) for allegedly being anticipated by WO 97/46253; hereinafter "'253"). Applicant disagrees with the Examiner's assertion that the present claims are anticipated by the following passage of '253:

> At pages 22, lines 22-25 WO97/46253 recites "[a]ncillary nucleic acid sequences coding for peptides known to stimulate, modify, or modulate a host's immune response, can be coadministered with the above-described antigens. Thus, genes encoding one or [sic] more of the various cytokines ..."

(Office Action page 9). In fact, '253 discloses constructs suitable for treatment of rheumatoid arthritis and multiple sclerosis, but is absolutely silent regarding whether such DNA vaccines might work as a treatment for autoimmune diabetes. In addition, by virtue of the indiscriminate recommendation that nucleic acid sequences encoding any peptide that stimulates, modifies or modulates a host's immune response would be suitable for inclusion in the prior art DNA vaccine, '253 fails to disclose selection of a biological response modifier for use in combination with a self-antigen that would be suitable for treatment or prevention of autoimmune diabetes.

Thus, '253 fails to disclose key elements of Applicant's compositions and methods, which all require that the autoimmune condition treated or prevented is "autoimmune diabetes" and that the biological response modifier is one that causes a positive regulatory immune response in the subject to which it is administered in conjunction with a self-antigen such as GAD or InsB. Accordingly, Applicant submits that '253 fails to disclose each and every element of amended claims 1-3, 5, 7-9, 14, 16-20, 22-24 and 26-30 and 32-38 would be required to constitute anticipation under 35 U.S.C. § 102(a).

In addition, Applicant respectfully submits that '253 would fail to suggest the invention constructs and methods for causing transient transfection of a polynucleotide encoding at least one self-antigen and a biological response modifier for use in treating or preventing diabetes, as required by amended claims 1, 11, and 22. '253 discloses treatment of multiple sclerosis, but is completely silent regarding prevention or treatment of diabetes. Accordingly, '253 provides no motivation to make or use a composition causing transient transfection for use in treating or preventing autoimmune diabetes, e.g., one wherein the self-antigen is a self-antigen associated with autoimmune diabetes. In addition, there is no suggestion in '253 how to modify the disclosed constructs and methods for use in treatment of autoimmune diabetes.

Autoimmune diseases differ considerably from each other, and other autoimmune diseases, such as multiple sclerosis and rheumatoid arthritis, differ considerably from autoimmune diabetes . Hence those of skill in the art understand that disclosure regarding other types of autoimmune disease cannot reasonably be extrapolated to pertain to treatment or prevention of autoimmune diabetes. For example, rheumatoid arthritis and multiple sclerosis affect categories of individuals with different genetic backgrounds than those who develop autoimmune diabetes. In addition, clinical trials have shown that non-overlapping categories of therapeutics may be effective against the inflammatory processes associated with these diseases. Preclinical models showed that whereas inhibition of co-stimulation suppresses inflammation associated with multiple sclerosis, it has an aggravating effect on evolution of diabetes (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=107957

41&dopt=Abstract; http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10605004&dopt=Abstract). In addition, Antibodies as well as T-cells are thought to be involved in multiple sclerosis; whereas antibodies do not play a pathogeneic role in autoimmune diabetes. Similarly, interferons appear to be beneficial in some clinical trials for lowering incidence and severity of certain forms of multiple sclerosis, whereas interferons have detrimental effects in autoimmune type 1 diabetes; a blockade of TNF in patients with rheumatoid arthritis is beneficial, but does not ameliorate the disease process in patients with autoimmune diabetes. In fact, TNF has been shown to have detrimental effects in pre-diabetic situations.

Yet, '253 is silent regarding such considerations. Therefore, Applicant respectfully submits '253 fails to suggest to those of skill in the art how to pick and choose among the disclosure of the reference to arrive at a construct and method of its use that would be beneficial in treatment or prevention of autoimmune diabetes.

Accordingly, Applicant submits that the '253 reference fails to disclose each and every element of the present claims, as would be required to establish anticipation under 35 U.S.C.§ 102, and fails to suggest the subject matter of the present invention so as to render the present claims *prima facie* obvious under 35 U.S.C.§ 103.

**C. WO 95/21926**

Applicant respectfully traverses the rejection of claims 1, 4, 11, 12, 15, 16, 22, 25, 26 30 and 32-36 and 30 under 35 U.S.C. § 102(b), for allegedly being anticipated by WO 95/21926 (hereinafter "'926").

By contrast to Applicant's invention as described above, '926 fails to disclose a nucleic acid sequence encoding both a biological response modifier and an epitope of a "self-antigen" as the term is understood in the art and as used in the Specification and claims herein. Instead, '926

discloses that a sequence encoding a" tolerogenic" epitope is to be placed at the N-terminus variable region of an immunoglobulin-encoding sequence. Applicants respectfully submit that an "immunoglobulin" as the term is used by '926 is not a "biological response modifier" as the term is used in Applicants' specification and claims and as understood by those of skill in the art. Rather an immunoglobulin is an antibody or a γ globulin. Thus, '926 fails to disclose each and every element of Applicants' amended claims 1, 11 and 22 as would be required to anticipation under 35 U.S.C. § 102(a).

In addition, Applicants respectfully submit that '926 fails to provide any motivation or suggestion to those of skill in the art how to modify of the disclosed construct to arrive at the invention construct and treatment methods. As the Examiner acknowledges, the disclosure of '926 pertains to a plasmid vector expressing myelin basic protein that is used in treatment of multiple sclerosis. '926 is completely silent regarding constructs useful for treatment or prevention of autoimmune diabetes in a subject, such as a human. In addition, '926 teaches that the prior art construct is expressed in a host cell and the expressed protein is administered to the animal's circulation as a fusion protein; whereas Applicant's composition is formulated for administration to the subject as a nucleic acid construct for transient expression by the subject (e.g. as a DNA vaccine). Hence, there is no suggestion in '926 to modify the prior art constructs and methods to arrive at Applicant's invention. Accordingly, Applicant submits that the '926 reference would also fail to suggest the subject matter of the present invention so as to render claims 1, 11 or 22 *prima facie* obvious under 35 U.S.C.§ 103.

**Conclusion**

In view of the above amendments and remarks, reconsideration and favorable action on claims 1-3, 5, 7-14, 16-24 and 26-38 are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: 12/28/00

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